REMARKS

Rejections under 35 U.S.C. 112, first paragraph, written description.

Claims 45, 51-65 and 69-78 are rejected under 35 U.S.C. 112, first paragraph, as the specification allegedly contains subject matter which was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors has possession of the claimed invention. The Examiner alleges that the recitation of "at about position 114" in Claim 45 is new matter as the specification allegedly does not provide a written description of nor sets forth the metes and bounds of the claimed subject matter.

Applicants traverse the rejection and note that support for the recitation of "at about position 114" can be found at p. 13, lines 16-20 of the specification which state:

> [t]he new analogs will have at least one new N-linked glycosylation site at any of positions 52, 53, 55, 86 and 114 and may further comprise additional N-linked or O-linked carbohydrate chains at other sites.

It is clearly contemplated in the disclosure that the positions of new glycosylation sites in human erythropoietin (Epo) are not limited to those that are exemplified and may encompass "about residue 114". Moreover, the metes and bounds of the phrase "about position 114" would be apparent to one skilled in the art.

It is requested that the rejection be withdrawn.

Claims 45-48 and 51-78 are rejected under 35 U.S.C. 112, first paragraph, as the specification allegedly does not provide sufficient written description to support the genus encompassed by the claims. The Examiner argues that the specification fails to place any limit on the number of amino acid changes that may be made to SEQ ID NO:1, fails to teach specifically any amino acid residues and whether the changes provide for N-linked or O-linked glycosylation.

The specification sets forth numerous positions for additional amino acid changes in addition to those specifically exemplified. For example, the specification teaches that one may add new N-linked

glycosylation sites at one or more of positions 30, 51, 57, 69, 88, 89, 136 and 138 (see p. 12, lines 19-21). Amino acid residues may be changed which are not likely to be involved in the binding of human Epo to its receptor. As disclosed at p. 15, lines 31-35, such residues may be identified by examination of the structure of the Epo-Epo receptor complex disclosed in Syed et al. (Nature 395, 511 (1998)). The specification also discloses that amino acid changes may include the introduction of both N-linked and O-linked glycosylation sites.

The Examiner cites in particular *Fiers v. Revel* 25 USPQ2d 1601 (Fed. Cir. 1993), *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ2d 1016 (Fed. Cir. 1991) and *Fiddes v. Baird* 30 USPQ2d 1481 (Fed. Cir. 1994) in support of the rejection. The case law can be distinguished on its facts from the present application. For example, in *Fiddes*, claims to all mammalian FGF's were being sought in view of a disclosure of only the amino acid sequence of bovine fibroblast growth factor (FGF). The extent of amino acid sequence disclosure in the claims at issue in these cases was far less than what is presently disclosed and, in a number of instances, the structure of the claimed proteins could not be readily recognized by one skilled in the art. In contrast, Claim 45 recites "one or more amino acid changes which provide for one or more additional glycosylation sites" in residues 1-165 of SEQ ID NO:1, which represents a set of amino acid changes which can be clearly recognized by one skilled in the art. Unlike the subject matter of the cited case law, the detailed chemical structure of a number of analogs of human Epo claimed in Claim 45 can be readily envisioned.

It is respectfully requested that the rejection be withdrawn.

Rejection under 35 U.S.C. 112, first paragraph, enablement.

Claims 45-48 and 51-78 are rejected under 35 U.S.C. 112, first paragraph, as the specification allegedly does not describe the claimed subject matter in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner argues that Claim 45 encompasses a new N-linked glycosylation site at about position 114, as well as additional glycosylation sites at other unspecified positions in SEQ ID NO:1. Claim 46 is deemed to encompass new N-linked glycosylation sites at any of positions 52, 53, 55, 86 and/or 114, as well as additional glycosylation sites at other unspecified positions in SEQ ID NO:1. The Examiner argues that specification lacks guidance and working examples regarding how to introduce a glycosylation site at any position in Epo, and further argues that scientific literature

relating to the introduction of new glycosylation sites in human Epo would not be obvious because of the unpredictability of the effects of mutations on Epo structure and function. In particular, the Examiner points to an alleged decrease in *in vitro* activity of certain Epo hyperglycosylated analogs (for example, analog N59) as evidence of such unpredictability.

Applicants respectfully traverse the rejection and maintain that the claims should not be limited simply to those Epo analogs having the amino acid changes necessary to add a new N-linked glycosylation site at about position 114 or at positions 52, 53, 55, 86 and/or 114. The specification enables far more than the specific analogs exemplified. For example, combinations of different N-linked glycosylation sites have been disclosed (see Table 2) and it would not require undue experimentation to make additional combination of new glycosylation sites. In addition, the disclosure of the three-dimensional structure of Epo complexed with its receptor (Syed et al. referred to above) provides important information to one skilled in the art regarding the location of amino acid residues in Epo which may be altered without perturbing protein structure and function. Thus the guidance in the specification combined with the knowledge available in the art as of the filing date clearly indicates that many hyperglycosylated Epo analogs having at least one new carbohydrate chain at about position 114 or at one of the specified positions may be prepared without undue experimentation.

The Examiner's allegation of unpredictability based upon the results of Table 2 is misleading. By focusing on the results of a single analog, N59, which was shown to have an *in vitro* activity of 25-75% of human Epo, the Examiner has ignored the clear disclosure of Table 2 that all but two of the analogs made and tested for *in vitro* activity retained activity equivalent to that of human Epo. The two analogs, N53 and N59, that did not exhibit full *in vitro* activity were found to retain a substantial portion (25-75%) of *in vitro* activity. The results in Table 2 cannot be taken as evidence of unpredictability. To the contrary, Table 2 clearly supports Applicants' position that the claimed analogs are enabled and may be made without undue experimentation.

It is requested that the rejection be withdrawn.

CONCLUSION

Claims 45-78 are in condition for allowance and an early notice thereof is solicited.

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